

THE CONSTITUTION
ERIODICTYOL, OF HOMOERIODICTYOL
AND
OF HESPERITIN

BY

FRANK TUTIN

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES
FREDERICK B. POWER, PH.D., LL.D., *Director*
6, King Street, Snow Hill
LONDON, E.C.

CCXVI.—*The Constitution of Eriodictyol, of Homoeriodictyol, and of Hesperitin.*

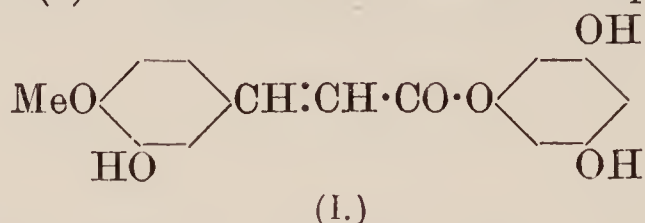
By FRANK TUTIN.

IN a paper communicated to the meeting of the American Pharmaceutical Association, held at Indianapolis, Ind., in September, 1906, Dr. F. B. Power and the present author described the isolation of two crystalline substances of phenolic nature from the leaves of *Eriodictyon Californicum* (Hooker and Arnott), Greene (*Proc. Amer. Pharm. Assoc.*, 1906, **54**, 352). These two compounds were designated eriodictyol and homoeriodictyol respectively, the former having been proved to possess the formula $C_{15}H_{12}O_6$, whilst the composition of the latter was shown to be $C_{16}H_{14}O_6$.

In a subsequent communication (*Trans.*, 1907, **91**, 887) it was noted that there are certain similarities in the properties of homoeriodictyol and its isomeride, hesperitin, which suggested that these two compounds were structurally related. Experiments supported this view, for, whilst hesperitin yields isoferulic acid (3-hydroxy-4-methoxycinnamic acid) and phloroglucinol on hydrolysis (Tiemann and Will, *Ber.*, 1881, **14**, 970), homoeriodictyol, when

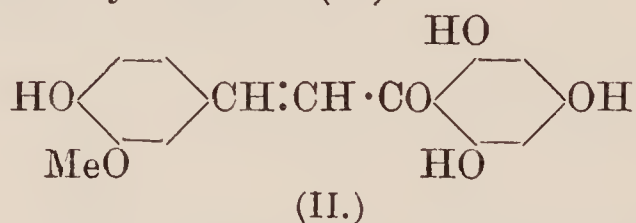
similarly treated, gave the same phenol together with ferulic acid (4-hydroxy-3-methoxycinnamic acid).

Tiemann and Will (*loc. cit.*) assigned to hesperitin the constitutional formula (I). This formula received support through the

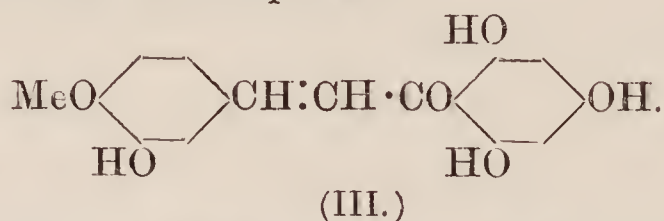


work of A. G. Perkin (Trans., 1898, **73**, 1037), who prepared acetylhesperitin, and recorded results which indicated that this compound was a triacetyl derivative.

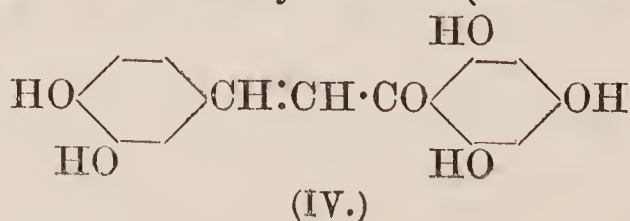
It appeared therefore from the results of the hydrolysis experiments mentioned above that homoeriodictyol differed from hesperitin only in the relative positions of the hydroxyl and methoxyl groups in the catechol part of the molecule. When, however, acetylhomoeriodictyol was prepared, it was found to contain four acetyl groups. It was therefore concluded that homoeriodictyol must be represented by formula (II).



From this it would appear that homoeriodictyol was not so similar to hesperitin in structure as had at first been concluded. Nevertheless, Dr. Power and the present author were so convinced of the near relationship of these two compounds that they ventured to suggest that the formula hitherto assigned to hesperitin is incorrect, notwithstanding the statement of Perkin (*loc. cit.*) that the latter yields only a triacetyl derivative. Formula (III) was therefore put forward for hesperitin.

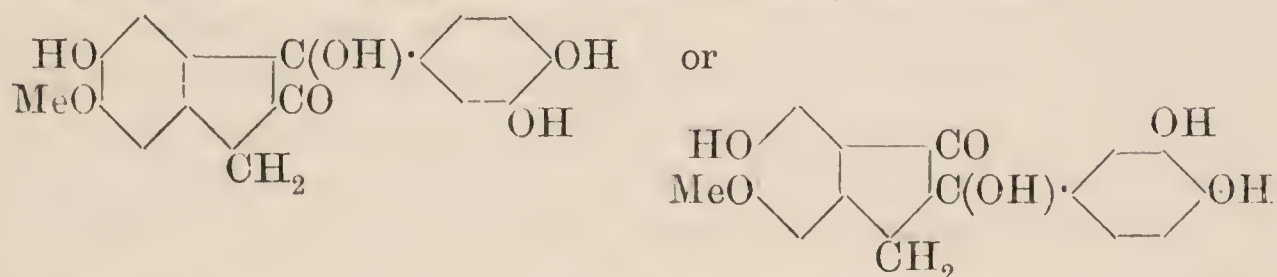


With regard to the constitution of eriodictyol, the amount of material which was at first available did not permit of many experiments being conducted with this substance, but the view was expressed that it was the parent compound of which hesperitin and homoeriodictyol are monomethyl ethers (formula IV).



Shortly after the appearance of the first paper by Power and Tutin on eriodictyon leaves (*loc. cit.*), a communication on the same subject was published by G. Mossler (*Annalen*, 1907, **351**, 233). This author recorded the isolation of a substance possessing the formula $C_{16}H_{14}O_6$, designated "eriodictyonon," which was evidently identical with homoeriodictyol. Mossler, however, did not succeed in isolating any eriodictyol.

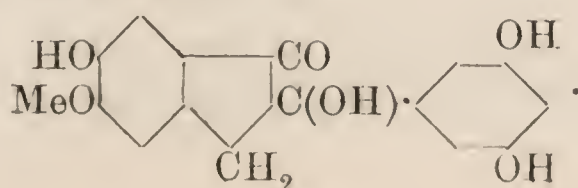
After having published the account of their work on the constitution of homoeriodictyol, Dr. Power and the present author received from Dr. Mossler a reprint of a paper communicated by him to the Academy of Sciences in Vienna (*Sitzungsber. K. Akad. Wiss. Wien*, 1907, **116**, ii, June, 1907). In this communication Mossler, who was unaware of the more recent work of the above-mentioned authors, admits that his "eriodictyonon" is identical with homoeriodictyol, and sets forth the conclusion that this substance is represented by one of the following formulæ:



This last publication by Mossler was replied to by Dr. Power and the present author (*Proc.*, 1907, **23**, 243), when it was pointed out that neither of the formulæ proposed by Mossler could be correct, since compounds possessing such a structure could not yield phloroglucinol.

One statement made by Mossler, however, was in direct conflict with the views which the present author, in conjunction with Dr. Power, had expressed regarding the constitution of homoeriodictyol, namely, that the substance in question was optically active. The last-mentioned authors were unable to confirm this, and, since the correctness of their conclusions regarding homoeriodictyol have now been fully proved, it is evident that the above statement of Mossler must have been based on an incorrect observation.

It appeared to the present author that there was one possible alternative to the formula which had been suggested by him in conjunction with Dr. Power for homoeriodictyol, but which was not at all probable, namely, a structure related to the second formula proposed by Mossler, as follows:



A substance possessing such a formula might conceivably yield, on hydrolysis, phloroglucinol and ferulic acid by the addition of two molecules of water, followed by the elimination of one such molecule, although such a change appeared highly improbable. It was considered advisable, therefore, in order conclusively to prove the constitution of homoeriodictyol and related compounds, to have recourse to synthetical experiments.

If the formulæ suggested by Dr. Power and the present author for eriodictyol, homoeriodictyol, and hesperitin be correct, then these substances are 2:4:6-*trihydroxyphenyl* 3:4-*dihydroxystyryl ketone*, 2:4:6-*trihydroxyphenyl* 4-*hydroxy-3-methoxystyryl ketone*, and 2:4:6-*trihydroxyphenyl* 3-*hydroxy-4-methoxystyryl ketone* respectively. It was decided therefore to methylate the first-mentioned three substances, and to compare the fully methylated products with synthetically prepared 2:4:6-*trimethoxyphenyl* 3:4-*dimethoxystyryl ketone*. The results of the methylation of eriodictyol, homoeriodictyol, and hesperitin are recorded in the present paper, and it is shown that each of them yields 2:4:6-*trimethoxyphenyl* 3:4-*dimethoxystyryl ketone* and 2-*hydroxy-4:6-dimethoxyphenyl* 3:4-*dimethoxystyryl ketone* identical in all respects with these substances as prepared synthetically (see the following paper).

The correctness of the formulæ suggested by Power and Tutin for eriodictyol, homoeriodictyol, and hesperitin is therefore proved beyond question.

Naringenin, a hydrolytic product of the glucoside, naringin, was shown by Will (*Ber.*, 1885, **18**, 1311) to be related to hesperitin. On heating with aqueous potassium hydroxide, it undergoes hydrolysis in a manner similar to the latter compound, and yields phloroglucinol and *p*-hydroxycinnamic acid. Will therefore concluded (*Ber.*, 1887, **20**, 297) that naringenin was the phloroglucinyl ester of the above-mentioned acid. In view of the results recorded in the present paper concerning hesperitin, there can be no doubt that naringenin is also a ketone, namely, 2:4:6-*trihydroxyphenyl* 4-*hydroxystyryl ketone*.

In a previous communication (Power and Tutin, *Trans.*, *loc. cit.*) a monomethyl ether of homoeriodictyol was described. A larger quantity of this substance has now been prepared, and it has been proved to be 2:6-*dihydroxy-4-methoxyphenyl* 4-*hydroxy-3-methoxystyryl ketone*. Similarly, when one methyl group is introduced into eriodictyol, it takes up the 4-position in the phenyl radicle, the product being a new isomeride of homoeriodictyol and hesperitin, namely, 2:6-*dihydroxy-4-methoxyphenyl* 3:4-*dihydroxystyryl ketone*.

The observation of Perkin (*loc. cit.*) regarding the anomalous character of the sodium derivative of hesperitin has been confirmed, this substance appearing to have the formula $C_{16}H_{13}O_6Na, C_{16}H_{14}O_6$. On the other hand, the statement made by Perkin that the product of the action of acetic anhydride on hesperitin is a triacetyl derivative cannot be confirmed, it having been proved that the substance thus formed is *tetra-acetylhesperitin*.

EXPERIMENTAL.

Eriodictyol (2: 4: 6-Trihydroxyphenyl 3: 4-Dihydroxystyryl Ketone).

A quantity (5 grams) of eriodictyol * was dissolved in alcohol, and an excess of methyl sulphate added, after which a concentrated alcoholic solution of potassium hydroxide was allowed to flow into the hot liquid at such a rate that the mixture was kept gently boiling. The liquid at first showed a tendency to darken, owing to the absorption of oxygen, but this soon ceased as methylation proceeded. Finally, the mixture assumed a dark red colour on the addition of the alkali, which only slowly disappeared. A further quantity of methyl sulphate was added, followed by more alkali, after which the mixture was kept for twenty minutes and then poured into water. The yellow product precipitated by this treatment was extracted by means of chloroform, the solution being washed, dried, and the solvent removed. The residue thus obtained was boiled with successive portions of dilute, aqueous potassium hydroxide so long as the decanted alkaline liquid was yellow in colour, after which the material insoluble in the alkali was washed and dissolved in alcohol. On inoculating the solution thus obtained with synthetic 2: 4: 6-trimethoxyphenyl 3: 4-dimethoxystyryl ketone (see the following paper), crystallisation rapidly ensued. The product so obtained was identical in all respects with the synthetical compound just mentioned. It crystallised in stout, pale yellow prisms, and, when dried in the air, melted at 85° , but in the anhydrous state at 117.5° :

0.1747 † gave 0.4279 CO_2 and 0.1046 H_2O . C = 66.8; H = 6.4.

$C_{20}H_{22}O_6$ requires C = 67.0; H = 6.1 per cent.

The potassium hydroxide extracts which had been decanted from the crude 2: 4: 6-trimethoxyphenyl 3: 4-dimethoxystyryl ketone were acidified, and the precipitated yellow product was crystallised from alcohol, in which it was rather sparingly soluble. Deep yellow

* For an improved method of isolating eriodictyol, homoeriodictyol, and other phenolic substances from *Eriodictyon* leaves, compare Tutin and Clewer, *Trans.*, 1909, 95, 81.

† Anhydrous substance.

leaflets were thus obtained, which melted at 154° , and were identical with the 2-hydroxy-4:6-dimethoxyphenyl 3:4-dimethoxystyryl ketone described in the following paper:

0.1279 gave 0.3099 CO_2 and 0.0680 H_2O . $\text{C}=66.1$; $\text{H}=5.9$.

$\text{C}_{19}\text{H}_{20}\text{O}_6$ requires 66.3; $\text{H}=5.8$ per cent.

Monomethyleriodictyol (2:6-Dihydroxy-4-methoxyphenyl 3:4-dihydroxystyryl ketone).—Four grams of eriodictyol were dissolved in absolute alcohol, and to this solution was added one and a-half molecular proportions of methyl sulphate, which had just previously been washed with aqueous sodium carbonate and dried. Slightly more than the equivalent amount of sodium, dissolved in absolute alcohol, was then gradually introduced into the hot mixture. After removing the alcohol, the residue was dissolved in ether, washed with water, and then fractionally extracted by shaking with successive portions of an aqueous solution of sodium carbonate. The first few extractions removed only unchanged eriodictyol, which formed the greater part of the product, but on acidifying the alkaline liquids subsequently obtained, a yellow product separated, which partly crystallised on keeping. This was collected, well washed with alcohol, and then recrystallised from this solvent, in which it was but sparingly soluble. Almost colourless needles were thus obtained, which melted at 215° :

0.1284 gave 0.2995 CO_2 and 0.0583 H_2O . $\text{C}=63.6$; $\text{H}=5.0$.

$\text{C}_{16}\text{H}_{14}\text{O}_6$ requires $\text{C}=63.5$; $\text{H}=4.6$ per cent.

This substance was therefore a *monomethyleriodictyol*, and since it is not identical with either homoeriodictyol (2:4:6-trihydroxyphenyl 4-hydroxy-3-methoxystyryl ketone) or hesperitin (2:4:6-trihydroxyphenyl 3-hydroxy-4-methoxystyryl ketone), and the hydroxyl group in the 2(or 6)-position is known to be difficult of methylation, it must be 2:6-dihydroxy-4-methoxyphenyl 3:4-dihydroxystyryl ketone.

Monomethyleriodictyol dissolves in aqueous alkali hydroxides, giving at first a practically colourless solution, but after about thirty seconds the liquid suddenly becomes totally black. On acetylation, monomethyleriodictyol yields a *tetra-acetyl* derivative, which forms colourless needles, melting at 159° .

Homoeriodictyol (2:4:6-Trihydroxyphenyl 4-Hydroxy-3-methoxystyryl Ketone).

The methylation of homoeriodictyol by means of methyl sulphate and potassium hydroxide proceeded analogously to that of eriodictyol, with the exception that there was no tendency to absorb oxygen, and consequently a cleaner product was obtained. The

methylated material was examined as above-described, when it readily yielded 2:4:6-trimethoxyphenyl 3:4-dimethoxystyryl ketone (m. p. 85° when air-dried; 117.5° when anhydrous), and 2-hydroxy-4:6-dimethoxyphenyl 3:4-dimethoxystyryl ketone (m. p. 154°).

Monomethylhomoeriodictyol (2:6-Dihydroxy-4-methoxyphenyl 4-hydroxy-3-methoxystyryl ketone). — Monomethylhomoeriodictyol, prepared by the action of methyl iodide on the crystalline sodium derivative of homoeriodictyol, was previously described by Power and Tutin (Trans., 1907, **91**, 895). A larger amount of this product has now been prepared by heating the above-mentioned sodium derivative with methyl iodide and methyl alcohol. The product thus obtained was dissolved in ether and freed from unchanged homoeriodictyol by extraction with dilute, aqueous sodium carbonate, after which the monomethylhomoeriodictyol was removed by shaking with a concentrated solution of this alkali. The product so obtained crystallised readily from alcohol in hard, yellow, wart-like masses, which melted at 142°.

On boiling monomethylhomoeriodictyol for several hours with 30 per cent. aqueous potassium hydroxide, hydrolysis occurred at the double linking, after which vanillin was readily isolated from the reaction mixture. It is evident from this, and considerations previously given, that the ONa group in the sodium derivative of homoeriodictyol, which is converted into methoxyl on treatment with methyl iodide, must occupy the 4-position in the phenyl group of the molecule. Monomethylhomoeriodictyol is therefore 2:6-dihydroxy-4-methoxyphenyl 4-hydroxy-3-methoxystyryl ketone.

Hesperitin (2:4:6-Trihydroxyphenyl 3-Hydroxy-4-methoxystyryl Ketone.)

Hesperitin, which is obtained by the hydrolysis of the glucoside, hesperidin, a constituent of the peel of the orange, lemon, and other related fruits, has been stated by Tiemann and Will (Ber., 1881, **14**, 970) to be the phlorogluciny ester of isoferulic acid. As stated in the introductory portion of this paper, however, the accuracy of this conclusion was doubted by Power and Tutin, and the present author has therefore further investigated the question.

Hesperitin, as obtained from Schuchardt, was recrystallised from ethyl acetate, when it melted at 224°, but when mixed with homoeriodictyol, fusion occurred at 200°. The material so obtained, however, did not agree in its characters with the description of hesperitin as given by A. G. Perkin (Trans., 1898, **73**, 1037). Thus it formed pale yellow plates, which could not be distinguished

by inspection from crystals of homoeriodictyol, it was practically tasteless,* and it dissolved in alkalis with a bright yellow colour. Perkin (*loc. cit.*), on the other hand, has described hesperitin as crystallising in almost colourless needles, possessing an intensely sweet taste, and dissolving in alkalis with, at the most, a faintly yellow colour. Nevertheless, the identity of the material employed by the present author with hesperitin cannot be doubted, inasmuch as the melting points of the compound itself and its acetyl derivative are in agreement with the corresponding constants given by Perkin for hesperitin and its acetyl derivative. Moreover, the substance yielded the abnormal sodium derivative, $C_{16}H_{13}O_6Na, C_{16}H_{14}O_6$, characteristic of hesperitin. (Found, $Na=3.8$. Calc., $Na=3.8$ per cent.)

Methylation of Hesperitin.

A quantity (1.5 grams) of hesperitin was methylated by means of potassium hydroxide and methyl sulphate in the manner previously described, when the reaction appeared to proceed precisely as in the case of homoeriodictyol. A good yield of product was obtained, which was readily separated into the two compounds similarly prepared from eriodictyol and its homologue, namely, 2-hydroxy-4: 6-dimethoxyphenyl 3: 4-dimethoxystyryl ketone (m. p. 154) and 2: 4: 6-trimethoxyphenyl 3: 4-dimethoxystyryl ketone (m. p. 85° when air-dried; 117.5° when anhydrous).

Tetra-acetylhesperitin.—Half a gram of hesperitin was boiled for three hours with a considerable excess of acetic anhydride, after which the greater part of the solvent was removed and the mixture diluted with ether. After several hours, a crystalline substance separated in tufts of colourless prisms, which melted at 120°. After recrystallisation from alcohol, this substance melted at 127°, and was evidently identical with the compound similarly prepared by Perkin (*loc. cit.*), which he regarded as a triacetyl derivative. The number of acetyl groups in the compound were estimated as follows. A quantity of the substance was hydrolysed with dilute potassium hydroxide, the mixture then acidified with sulphuric acid, and the acetic acid removed by a current of steam and titrated:

0.2616 gave acetic acid equivalent to 0.0900 NaOH. $CO \cdot CH_3 = 36.9$.

$C_{16}H_{10}O_6(CO \cdot CH_3)_4$ requires $CO \cdot CH_3 = 36.6$ per cent.

It is evident therefore that this compound was *tetra-acetylhesperitin*, and not a triacetyl derivative. This conclusion is in harmony with the properties of the substance, for it was insoluble

* Although hesperitin, when in the solid state, possesses no appreciable taste, its alcoholic solution is distinctly sweet.

in cold dilute sodium hydroxide, which would not have been the case had it contained a hydroxyl group, all the groups of this nature present in hesperitin having phenolic properties.

THE WELLCOME CHEMICAL RESEARCH LABORATORIES,
LONDON, E.C.

